Early Data from a Phase 2 Open Label Study of XEN007 (Flunarizine) for Treatment Resistant Absence Seizures

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Introduction

Absence seizures occur in several epilepsy syndromes, most commonly in childhood absence epilepsy (CAE)[1] . Ethosuximide (ESM), valproic acid (VPA) and lamotrigine (LTG) are first line therapy. Oscillatory burst firing in the corticothalamic circuit is considered the underlying mechanism of absence seizures mediated in part through low threshold transient calcium channels (T-type calcium channels)[2].

In a double blind, randomized clinical trial of ESM, VPA and LTG in 446 subjects with CAE, seizures were uncontrolled in >40% of subjects [3]. Thus, there is an unmet medical need for additional medications to treat refractory absence seizures.

Flunarizine is indicated for prophylaxis of migraine[4]. Flunarizine pharmacology primarily targets the blockade of calcium channels, including T-type calcium channels and sodium channels. At therapeutic doses, it is not known to affect the cardiovascular system. It has demonstrated efficacy in experimental models of absence seizures including both the pentylenetetrazole (PTZ) and gamma hydroxybutyrate (GHB) induced absence seizures in rats, when either administered independently or in combination with VPA and ESM[5].

Study Objectives

The objective of this ongoing open-label single centre study is to assess the efficacy, safety and tolerability of XEN007 in approximately 20 patients with treatment resistant absence epilepsy, who have failed two or more anti seizure medications (ASM) and are currently on a minimum of one appropriate ASM.

The primary outcome measure is percent reduction in 30-day absence seizure frequency for the final 30-days of treatment compared to the 30-day baseline period based on seizure diaries. A secondary endpoint is clinical EEG changes in patients as an objective measure of change in the number of absence seizures during EEG at visit 5 and impact on attention, anxiety, depression and quality of life between baseline and visits 4 and 5.

Methods

The study design is presented in Figure 1. The initial dose of XEN007 is 5mg/day. Dose escalation to 10 mg/day is at the discretion of the PI and performed at Visit 3.

Questionnaires used are:

- ADHD Rating Scale-IV,
- Quick Inventory of Depressive Symptomatology (Self-Report)
- Generalized Anxiety Disorder – 7 Items (Self-Report)
- Quality of Life in Childhood Epilepsy Questionnaire

Initially, patients with either Jeavons Syndrome or CAE (including those for whom CAE has persisted into adolescence) were enrolled. Based on these data, the study is now focused primarily on enrolling patients with CAE.

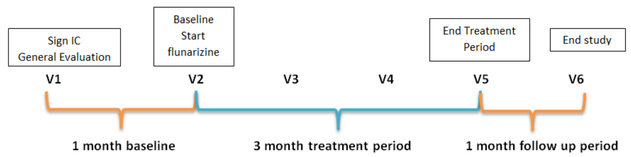
Results

Clinical and EEG data are summarized in Tables 1 and 2. No significant changes were observed in results of ADHD, depression, anxiety and QOL questionnaires pre and post-XEN007. Incidentally, whole exome sequencing was normal in patients 1, 3 and 5. Weight gain was the only significant adverse effect reported in one patient. Transient sedation was seen in 2 patients.

Table 1. Preliminary Demographics and Study Participant Overview

Patient / Sex	Epilepsy Syndrome	Age at Seizure Onset (y)	Age at Screening (y)	# of Failed ASMs	Current ASMs	Ketogenic Diet	Baseline Seizure Frequency/ Month	Seizure Frequency at 16 weeks	% Reduction in Seizures	Daily Dose of Flunarizine
1 F	Jeavons	5.5	16	7	VPA CLON	No	409	608	~50% increase	10 mg
2 F	Jeavons	6	14	6	VPA	Yes	334	N/A	Early Termination	5 mg
3 F	CAE	3	16	7	LTG ESM	Yes	41	6	85%	10 mg
4 F	CAE	7	15	3	LTG	No	79	34	57%	10 mg
5 F	CAE	2	5	2	VPA	No	54	9	83%	5 mg

Fig. 1. Summary Timeline of Visits and Treatment



The primary endpoint is the change in absence seizure frequency per 30 days between the baseline and the final 30-days of treatment.

Table 2. Number of Absence Seizures during Routine EEG

Patient #	Baseline	Visit 5	% Reduction in Seizures (EEG)
1	10	8	20
2	5	N/A	N/A
3	16	1	94
4	10	0	100
5	5	0	100

Discussion/Conclusions

- Flunarizine resulted in > 50% reduction in diary recorded seizures in all 3 CAE patients, with 2 showing >80% reduction.
- EEGs for the three CAE subjects showed resolution of absences for 2 subjects and 94% reduction for one.
- The two patients with Jeavons Syndrome did not respond to flunarizine. One had increased seizures and one terminated within one week due to increase in seizures.
- This evidence suggests that flunarizine could be a meaningful treatment for CAE patients experiencing persistent absence seizures.
- Flunarizine was well tolerated with weight gain as the only side effect in one patient resulting in medication discontinuation.
- Major limitations of this study include the very small number of subjects enrolled to date due to the impact of the global COVID-19 pandemic.
- Flunarizine plasma levels were not measured in this study.
- It is expected that this study will be expanded to include additional sites to enroll additional CAE subjects.
- In addition to the preliminary data presented here, topline results from a larger data set are expected to be available by the middle of 2021.

References / Bibliography

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